REMARKS

Claims 1, 2, and 4-13 are now in the application. Claims 1, 2, 10 and 11 have been amended to recite "adenosine and inorganic phosphate" in place of "adenosine". Basis for newly presented claim 13 can be found in the specification at page 7, lines 18-19. The amendments to the claims and newly presented claims do not introduce any new matter.

Claims 1, 2 and 4-12 were rejected under 35 USC 112, first paragraph. This rejection of the claims is not deemed tenable. Concerning enablement, the examiner's attention is kindly directed to page 8, lines 14-28 of the patent application, wherein it is stated that:

"After the release of the therapeutic composition of ATP in the small intestine, absorption of adenosine and inorganic phosphate-the catabolic products of ATP, or of ATP itself then follows. Absorption of ATP itself is followed by a rapid degradation to adenosine and inorganic phosphate inside the vascular bed (Slakey et al. 1990; Rapaport and Fontaine 1989; Rapaport and Fontaine 1989b). Both the adenosine and inorganic phosphate are then incorporated into the liver ATP pools (steady state levels), effectively expanding these pools (Rapaport and Zamecnik 1976; Rapaport and Fontaine 1989). The turnover of the expanded liver ATP pools, ATP pools which supply the adenosine precursor for red blood cell ATP synthesis, then lead to the expansion of red blood cell ATP pools. Expanded red blood cell ATP pools are in turn released from red blood cells into the blood plasma compartment (extracellular) via a non-hemolytic mechanism, where they are rapidly degraded to adenosine and inorganic phosphate (Slakey et al. 1990; Rapaport and Fontaine 1989; Rapaport 1990). The overall established mechanism thus provides for the slow, continuous release of adenosine in the blood plasma after the release of ATP at a preferred position along the distal part of the small intestine."

As discussed earlier in the prosecution of this application, the enablement for adenosine 5'-triphosphate (ATP), which is disclosed and taught in a non-limiting fashion, would indicate to the skilled artisan that adenosine and inorganic phosphate or adenosine 5'-monophosphate (AMP) are likely to possess similar activities in obtaining weight loss in humans. The reason is that these active agents undergo in vivo metabolism similar to

that of ATP. The same applies to magnesium 2+ compounds, which are similar in their properties of forming chelates or complexes with negatively charged phosphate groups. Moreover, it is well settled that to satisfy the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art. How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since the specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. See In re Marzocchi, , 439 F .2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971) . The specification of the instant application did not need to explicitly use adenosine 5'-monophosphate or adenosine and inorganic phosphate as adenosine generating agents ("adenosine active agents") since these activities were already well known in the art, although not for the claimed purposes. The use of magnesium 2+ compound is sufficient to teach the skilled artisan, who would be able to select a magnesium 2+ compound without undue experimentation in order to satisfy the requirements for claimed composition. (Please note the specification, page 7, lines 18-19).

"Stabilizers suitable for ATP disodium tablets are magnesium stearate, silica (SiO.sub.2)(Sylox), which are suitable stabilizers in small well-established amounts,").

The office action referred to four arguments in an attempt to justify the rejection.

In particular, the four arguments for the enablement rejection are:

1. "The nature of the invention, state and predictability of the art, and relative skill of those in the art."

The examiner cites Rapaport et al., who teach that administration of AMP or ATP to tumor-bearing mice resulted in the inhibition of host weight loss, rather than increased lipolysis resulting in weight loss. Further, since adenosine only has a blood plasma half-life of 3-6 seconds, how administration of AMP, ATP or adenosine "per 24 hours" will result in increased plasma levels of adenosine necessary to desensitize adenosine receptors. In response to this point raised, one must consider that in cachectic, weight losing ("wasting") tumor-bearing mice and subsequently in human clinical trials (Agteresch et al., copy enclosed) and larger ongoing human clinical

trials, administration of ATP inhibits weight loss in cachectic, weight losing (wasting) advanced cancer patients. The mechanism and target population are completely different from the mechanism of weight loss in normal, non-cachectic individuals after administration of ATP.

Cachectic tumor-bearing mice or cachectic advanced cancer patients do not have adipose tissue left and are losing mostly lean body mass. The desensitization by the generated adenosine is not a factor in the absence of triglycerides. Weight loss during cachexia is the result of enhanced gluconeogenesis, the synthesis of six carbon unit sugars from three carbon units such as alanine, glycerol or lactic acid, which occurs mostly in the liver. The six carbon unit sugar, glucose, is then utilized mostly by the tumor, producing a futile cycle which drains the hepatic energy stores and resulting in large weight losses. ATP acts in inhibiting weight loss by expanding liver ATP pools and inhibiting hepatic gluconeogenesis (see Table 1 in editorial in Drug Ther Perspect, copy enclosed).

Inhibition of weight loss in tumor-bearing mice according to Rapaport et al., and induction of weight loss by ATP in non-cachectic humans are two completely different inventions. Inhibition of gluconeogenesis in non-cachectic individuals by administration of ATP is a positive event in that it reduces blood sugar levels.

In addition, the ability of multiple, once daily, intraperitoneal injections to produce weight loss was questioned in the office action. Also, it was questioned as to how adenosine, with a short blood plasma half-life would produce increased levels of blood plasma adenosine. Adenosine as now recited in the claims is not administered without inorganic phosphate (see page 8, lines 14-28 of the specification). A combination of adenosine and inorganic phosphate is known in the art to produce elevated levels of blood plasma adenosine by mechanisms similar to those reported for AMP or ATP.

As to the issue of enablement, the examiner questions how would daily administration of ATP produce chronically elevated levels of adenosine in order to desensitize adipose A_1 adenosine receptors resulting in weight loss. Applicant encloses as Appendix 10, a publication by Rapaport entitled Mechanisms of Anticancer Activities of Adenine Nucleotides in Tumor-Bearing Hosts. Annals N.Y.

Academy of Sciences 1990; 603: 142-149 (cited as a reference in the present application, page 13, line 13). Please note Table 1 on page 146, the comparison of final body weight after ten consecutive days of ATP treatment. In groups of ten animals, NTB/ATP (non-tumor-bearing ATP group) lost about 5% of body weight compared to NTB/saline (non-tumor-bearing saline group). At that time, applicant was using these data only as a control related to the inhibition of weight loss in tumor-bearing hosts by administration of ATP. In calculating the statistical significance for this response to the office action, weight loss in the non-tumor-bearing ATP treated animals was statistically significant ($p<0.05$) as compared to non-tumor bearing saline treated animals. Considering the fact that these mice have very little adipose tissue, the results are meaningful, but at the time the mechanism of weight loss in non-tumor-bearing mice after administration of ATP was not understand, and there was no awareness of the statistical significance nor was there any reason to calculate such in comparison to saline treated non-tumor-bearing mice and was using the data as a control for other purposes.

In addition, the examiner states that Rapaport et al., was cited for evidentiary purposes (top of page 5 of office action). That is correct, however, Rapaport et al., was cited for evidentiary purposes regarding the mechanism of the generation of elevated levels of extracellular adenosine in blood plasma and not for evidentiary purposes related to weight loss after administration of adenine nucleotides (page 8, lines 18 and 26 of the specifications).

The sustained generation of adenosine after administration of adenosine and inorganic phosphate, AMP or ATP was discussed at length in applicant's response to the first enablement rejection of the claims of 04/25/06. In applicant's response of 07/24/06 it is stated (pages 7-8) that:

"With respect to the recitation concerning adenosine 5'-monophosphate, the specification is sufficient to teach those skilled in the art of the use thereof pursuant to the present invention. The specification discloses that the beneficial effect of the present invention is achieved by the cycling of adenosine and inorganic phosphate incorporation into liver ATP pools, the turnover of which supplies the adenosine precursor for expanded red blood cell ATP synthesis followed by release of red blood cell ATP into the

blood plasma compartment and the continuous degradation of blood plasma ATP pools to adenosine and inorganic phosphate. For example, please see page 8, lines 14-25 of the present specification. Once aware of the present disclosure, persons skilled in the art would appreciate that adenosine and inorganic phosphate or adenosine 5'-monophosphate or adenosine 5'-triphosphate are all effective in generating elevated levels of extracellular ATP, which in turn undergoes catalytic degradation to elevated levels of extracellular adenosine for the purposes of the present invention. For example, see U.S. Patent 5,227,371, which discloses active agents, the administration of which result in elevated blood plasma levels (extracellular) of adenosine 5'-triphosphate, which in turn undergoes continuous rapid degradation to adenosine. Adenosine and inorganic phosphate, adenosine 5'-monophosphate or adenosine 5'-triphosphate, when administered to a host, produce elevated levels of blood plasma (extracellular) adenosine 5'-triphosphate, which is degraded to (elevated levels of) adenosine by ectoenzymatic catabolic activities present in the vascular bed as well as enzymatic activities present in the blood plasma. Thus, the enablement for adenosine 5'-triphosphate (ATP), which is disclosed and taught in a non-limiting fashion, would indicate to the skilled artisan that adenosine and inorganic phosphate or adenosine 5'-monophosphate (AMP) are likely to possess similar activities in obtaining weight loss in humans. The reason is that these active agents undergo in vivo metabolism similar to that of ATP, as disclosed and taught in U.S. Patent 5,227,371, resulting in the elevation of blood plasma adenosine.

Furthermore, the fact that adenosine 5'-monophosphate as compared to adenosine is a better source of adenosine in vivo, has recently been confirmed by a clinical trial. The study started in October 2003, well after the PCT publication date of applicant's corresponding International application. A copy of the summary of the study purpose is enclosed (AMP as a Better Delivery System of Adenosine).

As demonstrated in U.S. Patent No. 5,227,371 and in the summary of a clinical trial of administration of AMP versus adenosine, the utilization of adenosine 5'-triphosphate in the instant specification was in a non-limiting fashion. Moreover, with regard to combinations of ATP and adenosine A1 receptor antagonists, the examiner's attention is kindly directed to Dagnelie PC and Beijer S, Clinical Nutrition Abstract, Vol.22, Suppl. 1, page S61, 2003 (copy enclosed).

Moreover, it is well settled that to satisfy the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art. How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since the specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. See In re Marzocchi, , 439 F .2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971) . The specifications to the instant application did not need to explicitly use adenosine 5'-monophosphate or adenosine and inorganic phosphate as adenosine generating agents ("adenosine active agents"), since these activities were already well known in the art, although not for the claimed purposes."

Thus, contrary to the administration of adenosine, which has a very short half-life, administration of adenosine and inorganic phosphate, AMP or ATP result in the cycling of ATP through the liver, red blood cells and blood plasma producing sustained elevation of blood plasma ATP and consequently elevated extracellular (blood plasma) adenosine pools. The blood plasma ATP pools are continuously degraded to adenosine and inorganic phosphate. The half-life of expanded red blood cell ATP pools is over six hours (in humans). Therefore, injections on subsequent days, continuous intravenous infusions or oral administration as demonstrated in the specification are known in the art to achieve sustained elevated levels of blood plasma adenosine.

Please also note that the language in the specification relates to a mechanism that occurs upon administering the claimed compounds, but is not required to set forth how to carry out the invention. The claims as presented recite the compounds that are administered for achieving the claimed results. Reciting anything more is not required by 35 USC 112. It is not necessary to claim why a particular result is achieved or its underlying mechanism, it is only necessary, as in the present claims, to claim what is to be done to achieve the claimed results.

2. "The breadth of the claims".

The examiner questions the broadest interpretation of the claims whereby the effects of eating carbohydrates, proteins or fats and consuming caffeine would contribute to muscle energy systems and therefore all contribute to ATP levels in the body. The answer to this query is that administration of adenine nucleotides (adenosine and inorganic phosphate, AMP or ATP) results in expansion of organ, blood and blood plasma ATP pools, which are steady state levels. Namely, the size of the pool does not take into account the turnover of ADP to ATP, which is the parameter affected by nutritional factors. Nutrients, after acting in converting ADP to ATP are stored mostly as fat (triglycerides) and contrary to direct administration of adenine nucleotides do not expand the pools of blood plasma adenosine. It is the pool size that determines the kinetic parameters of the interaction of ATP or adenosine with (extracellular) ecto-proteins, such as the adenosine receptors. There are three modes of action of nutrients in converting ADP to ATP, which is the currency of cellular energy. Two of the pathways take place in the mitochondria by oxidative phosphorylation (respiration) and the third pathway is by the breakdown of glucose, which can proceed anaerobically.

3. "The amount of direction or guidance provided and the presence of working examples."

The examiner concludes this rejection by stating that "There are no experimental methods described that would allow the skilled artisan to actually scientifically test whether adenosine receptors can be desensitized by exogenous administration of adenosine, ATP or AMP."

It is important to emphasize that the specification provides sufficient guidance to the skilled artisan, who can practice the invention without undue experimentation. For instance, skilled artisans were able to carry out clinical studies directly taught by the present invention after publication of applicant's PCT application. The point is demonstrated by the publications of Dagnelie PC and Beijer S and the "AMP as a Better Delivery System of Adenosine" clinical trial (copies of both enclosed). Dagnelie and Beijer demonstrated that in cancer patients (non-cachectic) chronic caffeine consumption showed a statistically significant correlation with increase in body mass. Thus, caffeine, which is an acknowledged lipolytic agent by its interactions with the A1 adenosine

receptor on adipose cells and antagonism of adenosine interaction with this receptor, when consumed chronically, desensitized the receptor to produce lipogenic effects (increase in fat mass). When ATP was administered to chronic caffeine consumers, adenosine acting as a lipolytic agent was able to reduce the effect of caffeine in desensitizing the A1 adenosine receptors on adipose cells (adipocytes) and the positive weight gaining effect of caffeine was absent. This publication demonstrates two points, one is that contrary to the examiner's assertion, the skilled artisan understand the present invention without undue effort or undue experimentation. Furthermore, skilled artisans other than applicant, experimentally confirm the adipose cells A1 adenosine receptor desensitization phenomenon after the submission of the present application.

The publication by Dagnelie PC and Beijer S (Does caffeine block the favorable effects of adenosine 5'-triphosphate (ATP) on the nutritional status of cancer patients; Clinical Nutrition 2003; vol. 22, supplement 1) is enclosed as a copy and was also submitted in applicant's response of 07/24/06 to the enablement rejections of 04/25/06. This publication demonstrates that skilled artisans other than applicant have applied the present invention and that the disclosure can be interpreted in the clinic.

The clinical trial entitled "AMP as a Better Delivery System of Adenosine" confirms the understanding of the skilled artisans that adenine nucleotides can produce sustained elevated levels of extracellular, blood plasma adenosine inside the vascular bed by mechanisms outlined earlier in this response, contrary to adenosine when administered alone, which has a very short half-life. This reference was also submitted with applicant's response of 07/24/06. As noted, these two references were submitted with applicant's response of 07/24/06 to the enablement rejection of 04/25/06 for the purpose of demonstrating no undue experimentation by skilled artisan. The following office action of 08/23/06 stated at the top of page 2 that "rejections and/or objections not reiterated from previous office actions are hereby withdrawn." It is important to note that the previous enablement rejection of 04/25/06 was similar to the recent enablement rejection of 03/23/07. Both office actions were structured along the eight factors of "re Wands".

4. "The quantity of experiments necessary."

The examiner states that the skilled artisan would not accept the assertion that administration of adenosine and inorganic phosphate, ATP or AMP and caffeine or

theophylline will lead to weight loss as taught and claimed by the specification. The publication by Dagnelie and Beijer clearly disputes this point. The examiner is stating that there is an absence of experimental evidence commensurate in scope with the claims. This statement is in contradiction to the statement on page 5 of this office action under "2. The breadth of the claims" whereby the examiner states that "the claims are reasonably narrow, reciting methods of inducing weight loss by administering caffeine (or theophylline) and AMP, ATP or adenosine (and inorganic phosphate)." If the claims are narrow, the experimental evidence supporting the claims need not be wide in scope. But that is not the issue here. Under points 3 and 4, the examiner seems to require that the specification include human clinical trial data that are sufficient for drug approval by the Food and Drug Administration (FDA). This is contrary to the accepted guidelines that patent teachings ought to use few illustrative examples or even descriptive terminology. This policy is designed to support rapid patenting of new ideas, since pivotal human trials take years to conduct, are very expensive and require patent protection in order to conduct.

Not only does the examiner require quantitative correlation of the data, which usually takes a large number of subjects to achieve, contrary to a few subjects (examples), which demonstrate qualitative aspects of the invention, but because of statistical methodology, a few subjects may not always yield quantitative correlations. This is precisely the reason why large pivotal drug approval human clinical trials have a large number of subjects. Finally, the examiner complains that data was not generated with a control group that did not take ATP (control group or placebo) (last statement of point 4). Even phase II human clinical trials for drug approval by the FDA, which are designed to determine efficacy, do not usually have a control or placebo arm. Only pivotal human trials are required in most cases to have a placebo arm. At that time of course, an invention would have been published by the clinical investigators, years would have passed since the demonstration of the original idea and patent applications would no more be relevant or even possible.

Furthermore, please see MPEP 2100 which clearly addresses this issue:

"Utilities - 2100 Patentability

2107.03 Special Considerations for Asserted Therapeutic or Pharmacological Utilities

The Federal courts have consistently reversed rejections by the Office asserting a lack of utility for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence that reasonably supports such a utility. In view of this, Office personnel should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility.

I. A REASONABLE CORRELATION BETWEEN THE EVIDENCE AND THE ASSERTED UTILITY IS SUFFICIENT

As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980)."

Furthermore, the opening statement of the present enablement rejection arguments (top of page 3 of the last office action) is:

"To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation", the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of

the claimed invention. PPG v. Guardian, 75 F.3d 1558,1564 (Fed. Cir. 1996)". ("As pointed out by the court *In re Angstadt,* 337 F.2d 498 at 504 (CCPA 1976), the key word is "undue" not "experimentation").

This statement does not support rejection arguments 3 and 4 in the recent office action, as was argued earlier in this response.

Finally it is instructive to consider, the prior prosecution in the application along with the guidelines to be observed by the Office in examining patent applications. For instance, Under MPEP 2100 Patentability, it is stated:

"2164.04 Burden on the Examiner Under *>the< Enablement Requirement [R-1]

In accordance with the principles of compact prosecution, if an enablement rejection is appropriate, the first Office action on the merits should present the best case with all the relevant reasons, issues, and evidence so that all such rejections can be withdrawn if applicant provides appropriate convincing arguments and/or evidence in rebuttal. Providing the best case in the first Office action will also allow the second Office action to be made final should applicant fail to provide appropriate convincing arguments and/or evidence. Citing new references and/or expanding arguments in a second Office action could prevent that Office action from being made final. The principles of compact prosecution also dictate that if an enablement rejection is appropriate and the examiner recognizes limitations that would render the claims enabled, the examiner should note such limitations to applicant as early in the prosecution as possible.

In other words, the examiner should always look for enabled, allowable subject matter and communicate to applicant what that subject matter is at the earliest point possible in the prosecution of the application."

In the office action of 10/05/06 (page 4) the examiner states:

"Therefore, only theophylline and caffeine, but not the full breadth of the claims, meets the written provision description of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes it clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision (see *Vas-Cath* at page 115). See also *In re Barker,* 559F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be

sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement)."

Thus, the examiner clearly and unequivocally stated that the prosecution on the merit regarding enablement was closed to his satisfaction, except for the issue of the adenosine receptor antagonists.

However, in the present office action of 03/23/07, the examiner lists four reasons for the enablement rejections, which are an expansion of the enablement rejections of the office action of 04/25/06 (copy enclosed). The enablement rejections of 04/25/06 were deemed responded to by applicant on 07/24/06. The next office action of 08/23/06 was termed a final action and required applicant or attorney **only** to submit a Terminal Disclaimer, which was filed on 09/05/06. Once the final rejection was overcome by the requested submission of the Terminal Disclaimer, the examiner applied new ground of rejection in the non-final office action of 10/05/06.

It is important to note that under MPEP 706.07(e) (Withdrawal of Final Rejection, General) it is stated that: "The examiner may withdraw the rejection of finally rejected claims. If new facts or reasons are presented such as to convince the examiner that the previously rejected claims are in fact allowable or patentable in the case of reexamination, then the final rejection should be withdrawn. Occasionally, the finality of a rejection may be withdrawn in order to apply a new ground of rejection.
Although it is permissible to withdraw a final rejection for the purpose of entering a new ground of rejection, this practice is to be limited to situations where a new reference either fully meets at least one claim or meets it except for differences which are shown to be completely obvious. Normally, the previous rejection should be withdrawn with respect to the claim or claims involved.
The practice should not be used for application of subsidiary references, or of cumulative references, or of references which are merely considered to be better than those of record."

The examiner withdrew a final rejection for the purpose of entering a new ground of rejection, initially without introducing any new reference (in the office action of 10/05/06). Subsequently to applicant response of 11/02/06, which complied with all of the examiner's requests to the letter, the examiner further introduced an additional

unrelated new ground of enablement rejection with a newly mentioned reference, which is not new since it was introduced in the original application and was a reference of record.

This reference cited by applicant in the original application is Rapaport et al., (bottom of page 4 of office action). This reference however, is totally and unequivocally irrelevant to the grounds of rejection introduced in the recent office action as discussed below.

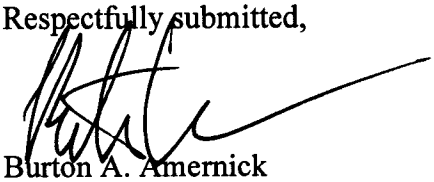
In view of the above amendment, applicant believes the pending application is in condition for allowance.

In the event the Examiner believes an interview might serve in any way to advance the prosecution of this application, the undersigned is available at the telephone number noted below.

The Office is authorized to charge any necessary fees to Deposit Account No. 22-0185.

Dated: July 19, 2007

Respectfully submitted,



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